REMARKS

Claim 2 has been amended to positively recite the unobvious steps of (a) transdermally administering anagrelide to a patient, (b) minimizing the amount of first pass liver metabolism of the anagrelide to 3-hydroxy anagrelide in the patient, (c) reducing the plasma concentration of 3-hydroxy anagrelide in the patient, (d) reducing the amount of PDEIII inhibition by 3-hydroxy anagrelide in the patient, and (e) reducing the cardiovascular side-effects caused by PDEIII inhibition in the patient. Claims 3, 6-9, 14, 15, 23-34, 36, and 50 have been cancelled.

Support for step (b) of claim 2 can be found on page 2, lines 25-31, page 4, line 30 to page 5, line 4, page 5, line 26 to page 6, line 3, in Example 8 starting on page 30, line 20 and in Example 11 starting on page 34, line 9 of the application as filed. The structure of "Metabolite A," described in Example 11 as producing cardiovascular side effects, is provided on page 31 in Example 8 and has the chemical name "3-hydroxy anagrelide." Thus, "3-hydroxy anagrelide" can be substituted for the phrase "metabolites exhibiting cardiovascular and/or inotropic side effects" disclosed on page 5, lines 30-31. Support for step (d) of claim 2 can be found in Example 9 starting on page 33, line 1. Support for step (e) of claim 2 can be found on page 2, lines 25-31 and page 35, lines 15-20. No new matter has been added by way of these amendments.

After entry of these amendments, the total claim count has been reduced to 9 (claim 2 and claims 12, 13, and 17-22 that depend from claim 2).

Examiners' Interview conducted June 3, 2009

Applicant appreciates the time spent by Examiner Hughes and Examiner Henley to discuss this application with the undersigned. Statements made in the Office Action mailed April 1, 2009, proposed claim amendments, and recently submitted Information Disclosure Statements were discussed. Examiner Hughes expressed her concern that, at the time of filing the application, transdermal administration was generally known to circumvent first pass liver metabolism. The undersigned was encouraged to submit an amendment to address these issues.

First Rejection under 35 U.S.C. §103(a) – Obviousness

Claims 2, 3, 6-9, 12, 17-20, 26, 27, 32, 36, and 50 remain rejected as obvious over U.S. Patent No. 6,194,420 ("Lang") in view of U.S. Patent No. 6,221,383 ("Miranda") and in further view of U.S. Patent No. 6,024,975 ("D'Angelo"). The Examiner asserts that Lang teaches anagrelide containing pharmaceutical compositions to treat essential thrombocythemia. According to the Examiner, Miranda describes the transdermal administration of anagrelide. The Examiner asserts that D'Angelo teaches the transdermal delivery of drugs using a patch system. The Examiner contends that one of ordinary skill in the art would be motivated to combine the teachings of Lang with the teachings of Miranda because both describe the administration of anagrelide as part of a pharmaceutical composition. The Examiner further asserts that one skilled in the art would combine the teachings of Lang, Miranda, and D'Angelo because when the teachings of Lang and Miranda are combined, these teachings overlap with D'Angelo in subject matter, *i.e.*, the administration of medicaments, particularly anagrelide, by transdermal delivery.

Second Rejection under 35 U.S.C. §103(a) – Obviousness

Claims 21-23 and 28 and 30 remain rejected as obvious over Lang in view of D'Angelo and further in view of U.S. Patent No. 5,133,972 ("Ferrini"). The Examiner incorporates by reference the discussion of Lang and D'Angelo from the above rejections. Ferrini, according to the Examiner, teaches a multilayered therapeutic system for the transdermal administration of an active ingredient. The Examiner asserts that a skilled artisan would be motivated to combine Lang, D'Angelo, and Ferrini because each describes the administration of medicaments by transdermal delivery.

In both of these obviousness rejections, the Examiner asserts that Applicant's previous arguments "do not go to the heart of the language that is the present contemplation in the claims," therefore Applicant's arguments were not assigned patentable weight. *See* pages 3 and 4 of the Office Action.

Response to the First and Second Obviousness Rejections

Applicant has amended the claims to expressly recite the unobvious and unexpected features of the instant invention.

- Step (e) of amended claim 2 recites the unexpected result that the adverse cardiovascular side-effects observed in patients orally administered anagrelide are reduced in a patient who is transdermally administered anagrelide.

- The reduction in cardiovascular side-effects results from a reduction in the amount of PDEIII inhibition by 3-hydroxy anagrelide observed in transdermally administered patients compared to patients who are orally administered anagrelide as set forth in step (d) of amended claim 2. Inhibition of PDEIII is known to increase both the force and rate of cardiac contractility as discussed in Example 9 on page 33, lines 2-5 of the application as filed.

- The reduction in PDEIII inhibition by 3-hydroxy anagrelide results from a reduction in the plasma concentration of 3-hydroxy anagrelide in transdermally administered patients compared to patients who are orally administered anagrelide as recited in step (c) of amended claim 2.

- The reduction in plasma concentration of 3-hydroxy anagrelide results from a reduction in the amount of first pass liver metabolism of anagrelide to 3-hydroxy anagrelide in a transdermally administered patient compared to a patient who is orally administered anagrelide as recited in step (b) of amended claim 2.

- The minimization of first pass liver metabolism of anagrelide to 3-hydroxy anagrelide results from the transdermal administration of anagrelide as recited in step (a) of amended claim 2.

The invention expressly recited in the claims is not merely a predictable use of prior art elements according to their established function and, therefore, is not obvious. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) and MPEP §2121(I). Prior to

Applicant's invention, one of ordinary skill in the art would have predicted that cardiovascular side-effects would be observed in a patient transdermally administered anagrelide similar to orally administered patients. The prior art neither discloses nor suggests a positive correlation between avoiding the first pass liver metabolism of anagrelide using transdermal administration and the disappearance of adverse cardiovascular side-effects. To the contrary, as discussed below, first pass liver metabolism is associated with detoxification.

Surprisingly, however, Applicant discovered that transdermally administering anagrelide to treat thrombocythemia minimizes the adverse cardiovascular side-effects observed when anagrelide is administered orally as positively recited as steps in the claims. These unpredictable results are discussed in the response filed September 19, 2007, the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Richard Franklin ("the Franklin Declaration") filed September 19, 2007, the response file March 28, 2008, the response filed August 1, 2008, and the response filed February 10, 2009.

These responses and Dr. Franklin's Declaration explain that Applicant determined the surprising cause of the adverse cardiovascular side-effects: 3-hydroxy anagrelide. Transdermal administration of anagrelide minimizes the amount of 3-hydroxy anagrelide formed during first-pass liver metabolism as recited in step (b). Transdermal administration of anagrelide reduces the plasma concentration of 3-hydroxy anagrelide as recited in step (c). Transdermal administration of anagrelide reduces the inhibition of phosphodiesterase III (PDEIII, an enzyme known to affect the cardiovascular system) by 3-hydroxy anagrelide as recited in step (d). Transderaml administration of anagrelide reduces adverse cardiovascular side-effects as recited in step (e). The above-listed responses and Dr. Franklin's Declaration provide 2 reasons for the non-obviousness of Applicant's invention. First, 3-hydroxy anagrelide inhibited PDEIII to a greater than expected degree in view of the relatively minor change to the structure of anagrelide (*i.e.*, 3-hydroxy anagrelide inhibited PDEIII 40 times more potently than anagrelide). Second, the fact that the 3-hydroxy anagrelide metabolite causes undesirable side-effects represents the opposite of the expected metabolic detoxification process occurring in the liver.

Notwithstanding the Examiner's assertion that the prior art generally discloses the reduction in first pass liver metabolism by transdermal administration, the presently claimed invention is not obvious because one of ordinary skill in the art would not have expected a reduction in cardiovascular side-effects as a consequence of transdermal administration.

Moreover, notwithstanding the Examiner's assertion that that anagrelide treats thrombosis by reducing the number of blood platelets and thrombocythemia is a condition in which a patient has an excess of platelets, thrombosis and thrombocythemia are distinct conditions as discussed in previous responses and, in particular, in the Declaration pursuant to 37 C.F.R. §1.132 by Gunnar Birgegård, M.D., Ph.D. submitted on February 10, 2009. Despite any similarities that the Examiner may find between the two conditions, the presently claimed invention, based on the surprising finding that transdermally administered anagrelide minimizes the adverse cardiovascular side effects observed in patients who are orally administered anagrelide, would not have been predictable and, thus, not obvious as discussed above.

For at least the reasons provided above, Applicant respectfully requests withdrawal of the first and second obviousness rejections.

Third Rejection under 35 U.S.C. §103(a) – Obviousness

Claims 24-25, 29, 31, 33-34, and 36 remain rejected as obvious over Lang in view of D'Angelo and in further view of U.S. Patent No. 4,847,276 ("Yarrington"). This obviousness rejection has been mooted by cancellation of these claims. Withdrawal of this obviousness rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered, that the response be entered, and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could

be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: July 20, 2009

Respectfully submitted,

By _____

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